REMARKS

The Applicants wish to thank the Examiner for participating in the June 15, 2005 telephone interview and for her helpful comments. A 37 C.F.R. §1.133 Applicants' Interview Summary is submitted separately.

Oath/Declaration

The Examiner objects to the submitted 37 C.F.R. §1.63 oath as allegedly being non-compliant pursuant to 37 C.F.R. §1.52(c) because non-initialed and/or non-dated alterations were made to the oath.

The Applicants acknowledge the Examiner's objection to the oath as being non-compliant pursuant to 37 C.F.R. §1.52(c) and are endeavoring to procure a new oath. However, this will require more time as several of the inventors reside in England and Ireland. The Applicants wish to assure the Examiner that once received, the new oath will be promptly submitted.

Amendments to the Specification

The Abstract was amended to replace "comprising" with "that comprise" for grammatical reasons. The Applicants respectfully request the withdrawal of the Examiner's objection.

Amendments to the Claims

The Applicants respectfully ask the Examiner to replace all prior versions and listings of claims in the present application with the listing of claims currently provided. Claims 38-47 are new, Claims 20-28, 32-33 were amended and Claims 29-31 and 35-37 were cancelled. Claims 1-19 and 34 were cancelled in a previous reply. The Applicants state that all new and amended claims do not add new subject matter to the present specification.

Support for the plasmid embraced by Claims 20 and 40 and the claims depending from these two independent claims can be found throughout the present specification., such as, *e.g.*, on page 7, 26-27; page 8, lines 1-27; page 9, lines 1-3; page 11, lines 1-11; page 12, lines 1-27; page 13, lines 1-5; page 17, 1-3.

1. Independent Claim 20 recites, in part, a "clostridial neurotoxin heavy chain" instead of a "binding element" and a "clostridial neurotoxin heavy chain" instead of a "translocation element." Support for both embodiments can be found, *e.g.*, on page 7, 26-27 through page 8, lines 1-1; page 8, lines 1-3; page 11, lines 1-11; page 12, lines 1-9; and original claims 2, 7 and 23.

2. Independent Claim 40 recites, in part, a binding element that "preferentially interact with sensory afferent neuron cell surface marker" instead of a binding element that preferentially interacts with any "target cell surface marker" and support for this embodiment can be found, *e.g.*, on page 8, lines 15-19; page 13, lines 3-5; page 17, 1-3; and original claims 10 and 30. In addition Claim 40 recites, in part, a "clostridial neurotoxin heavy chain" instead of a "translocation element" and a "clostridial neurotoxin light chain" instead of a "therapeutic element." Support for both embodiments can be

found, *e.g.*, on page 7, 26-27 through page 8, lines 1-1; page 8, lines 1-3; page 11, lines 1-11; page 12, lines 1-9; and original claims 2, 7 and 23.

3. Claims 39 and 47 recite specific protease cleavage sites and support for this embodiment can be found, *e.g.*, on page 18, lines 13-23 and the Sequence Listing.

Rejection Pursuant to 35 U.S.C. §112, ¶2 Indefiniteness

The Examiner has rejected Claims 32 and 33 as allegedly lacking definiteness under 35 U.S.C. §112, ¶2 stating that the limitation "derived from a clostridial neurotoxin" lacks antecedent basis. The Applicants respectfully ask for reconsideration under 37 C.F.R. §1.111.

The Applicants have amended Claims 32 and 33 by deleting the phrase "derived from a clostridial neurotoxin". The Applicants respectfully submit that Claims 32 and 33 now have proper antecedent basis and request withdrawal of the 35 U.S.C. §112, ¶2 indefinite rejection.

Rejection Pursuant to 35 U.S.C. §102(b) Anticipation

The Examiner has rejected Claims 20, 23-29, 32 and 35-37 as allegedly anticipated under 35 U.S.C. §102(b) by PCT patent publication WO98/07864, Clifford C. Shone *et al.*, Recombinant Toxin Fragments, Feb. 26, 1998 ('864 publication). Specifically, the Examiner contends that the '864 publication discloses a binding element that reads on the present claims. The Applicants respectfully ask for reconsideration under 37 C.F.R. §1.111.

According to *MPEP* §2131, for a reference to anticipated a pending claim, that reference must teach each and every element of the pending claim. The present Claim 20 recites, in part, a "clostridial neurotoxin heavy chain" instead of a "binding element." The recombinant single-chain toxins disclosed in '864 publication lack a clostridial toxin binding element (the H_C domain) and, therefore, cannot anticipate the pending claims. For example, on page 3, last paragraph, last four lines, the '864 publication states:

> Accordingly, the invention may thus provide a single polypeptide chain containing a domain equivalent to a clostridial toxin light chain [therapeutic element] and a domain providing the functional aspects of the H_N of a clostridial toxin heavy chain [translocation element], ***whilist lacking the functional aspects of a clostridial toxin H_C domain*** [binding element].

In addition, while the '864 publication discloses recombinant toxins having a binding element, such binding elements are described in the context of a "polypeptide comprises a non-clostridial sequence that binds to a cell surface receptor," see page 8, first paragraph, first two lines. Similar disclosure can be found elsewhere in the '684 publication, *e.g.*, on page 7, entire second paragraph; page 7, last paragraph through page 8, first paragraph; page 8, last paragraph, lines 3-8.

Claims 23-29, 32 are all dependent on Claim 20, and as such, also recite a "clostridial neurotoxin heavy chain" instead of a "binding element." Thus, the '864 publication does not read on these claims for the reasons given above for Claim 20.

The cancellation of Claims 35-37 renders the anticipation rejections directed towards these claims as immaterial, and thus are not addressed in the Applicant's Reply.

Thus, the '864 publication does not anticipate the pending claims because the '864 publication does not teach a recombinant toxin comprising a clostridial toxin binding element. Therefore, the Applicants respectfully submit that the pending claims of the present application are novel and not anticipated by the '864 publication and respectfully request withdrawal of the 35 U.S.C. §102(b) anticipation rejections for Claims 20, 23-29, 32 and 35-37.

Rejection Pursuant to 35 U.S.C. §102 (e) Anticipation

The Examiner also rejects Claim 20, 23-29 and 33 as allegedly anticipated by U. S. patent US 6,461,617, Clifford C. Shone *et al.*, Recombinant Toxin Fragments, Oct. 8, 2002 ('617 patent). The '617 patent is the U.S. national patent application stemming from the PCT patent publication WO98/07864 discussed above. As such, the '617 patent discloses essentially identical subject matter to the '864 publication and the reasons for rejection are likewise identical. The Applicants respectfully ask for reconsideration under 37 C.F.R. §1.111.

The Applicants grounds for disagreement are also the same as indicated above for the '864 application. The '617 patent does not teach recombinant toxin containing a clostridial toxin binding element and, thus, the '617 patent cannot anticipate the pending claims of the present application. Therefore, the Applicants respectfully submit that the pending claims are novel and not anticipated by the '617 patent and respectfully request withdrawal of the 35 U.S.C. §102(e) anticipation rejections for Claims 20, 23-29, 32 and 35-37.

Rejection Pursuant to 35 U.S.C. §103(a) Obviousness

The Examiner has rejected Claims 20-29 and 31-33 as allegedly obvious under 35 U.S.C. §103 over the '617 patent. Specifically the Examiner argues that the '617 patent mentions an invention that can be practiced with both botulinum and tetanus toxins. The Applicants respectfully ask for reconsideration under 37 C.F.R. §1.111.

According to *MPEP* §2143, to render a pending claim obvious, a reference must expressly or impliedly teach or suggest the claimed subject matter. The Applicant's respectfully submit that Claims 20-29 and 31-33 recite, in part, a "clostridial neurotoxin heavy chain binding element able to preferentially interact with a target cell surface marker." A clostridial neurotoxin binding element is specifically taught away from in the '614 patent. This teaching away demonstrates a lack of *prima facie* obviousness and, therefore, the pending claims cannot be obvious over the '617 patent. For example, the '617 patent directly teaches that a recombinant toxin should lack the "functional aspects of a clostridial toxin H_C domain [*i.e.*, the binding element]," see col 2, lines 44-49. On col 4, lines 57-63, the '617 patent similarly states that the recombinant toxins of the invention should lack the portion of the clostridial toxin heavy "responsible for binding of toxin to cell surface receptors" and that it is "preferred that such a polypeptide lacks the intact portion designated H_C of a clostridial toxin heavy chain." Furthermore, in the context of describing which binding elements are useful for targeting a recombinant toxin to a desired cell, the '617 patent states that such a binding

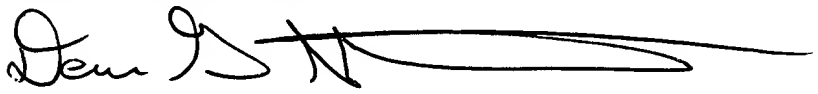
element "comprises a non-clostridial sequence that binds to a cell surface receptor," see col 5, lines14-15.

Thus, based on the teaching away in the '617 patent of a recombinant toxin containing a clostridial neurotoxin heavy chain binding element, a *prima facie* obviousness case cannot be made. Therefore, the Applicants respectfully submit that nothing in the '617 patent discloses or suggests the claimed invention in the present application and respectfully request withdrawal of the 35 U.S.C. §103(a) obviousness rejection for Claims 20-29 and 31-33.

CONCLUSION

For the above reasons the Applicants respectfully submit that the claims are in condition for allowance, and the Applicants respectfully urge the Examiner to issue a Notice to that effect. Please use Deposit Account 01-0885 for the payment of the extension fees or any other fees due in connection with the current response.

Respectfully submitted,



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